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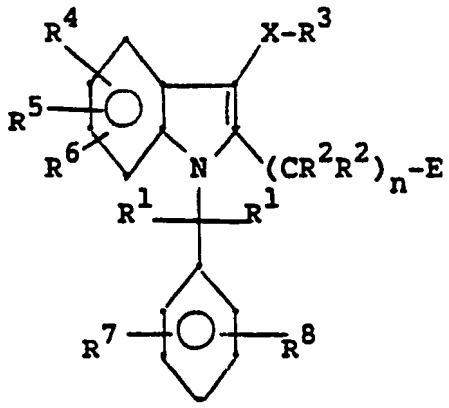
(54) 3-hetero-substituted-N-benzyl-indoles.

(57) Compounds having the formula:



are inhibitors of leukotriene biosynthesis. These compounds are useful as anti-asthmatic, anti-allergic, anti-

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3-HETERO-SUBSTITUTED-N-BENZYL-INDOLES

BACKGROUND OF THE INVENTION

The leukotrienes and their biological activities, especially their roles in various disease states and conditions have been described. For example, see EP 140,684 (May 8, 1985), which is incorporated herein by reference.

Several classes of compounds exhibit ability to inhibit the biosynthesis of leukotrienes in mammals, especially humans.

See, for example, EP 166,591 (January 2, 1986). The compounds of the present invention are distinguished from those of EP 166,591 in the important feature of possessing a heteroatom at position 3 in place of a hydrogen or carbon substituent. The heteroatom introduces unique electronic and chemical properties into the indole nucleus. The compounds of the present invention are further distinguished in that they uniquely inhibit the biosynthesis of leukotrienes, whereas those of EP 166,591 are antagonists of prostaglandins which also possess leukotriene biosynthesis inhibitory properties.

CH-A 454,858 and CH-A-455,777 teach derivatives of indole-2-acetic acid as useful for the treatment of inflammatory deseases. The compounds of these two Swiss patents are distinguished from those of the present invention by the same chemical differences as in EP 166,591, as well as by differences in the scope of their biological activities.

Walton et al., J. Med. Chem., 11, 1252 (1968) teach certain indole-3-acetic acid derivatives assayed for tumor chemotherapy activity. Walton et al. teach compounds with an alkanoic acid in the 3-position, rather than in the 2-position, and they also lack a heteroatom substituent. The single compound of Walton et al. with a 2-alkanoic acid also lacks a 3-hetero substituent. Walton et al. disclose no useful biological activity for their indole 2-alkanoic acid.

JP-238017 teaches 3-substituted-2-phenyl-indole derivatives as having lipoxygenase and cyclooxygenase inhibiting activity. In addition to the important differences in biological activities, these compounds possess a phenyl group in the 2-position and are lacking the N-benzyl substituent of the compounds of the present invention.

SUMMARY OF THE INVENTION

The present invention relates to compounds having activity as leukotriene biosynthesis inhibitors, to methods for their preparation, and to methods and pharmaceutical formulations for using these compounds in mammals (especially humans).

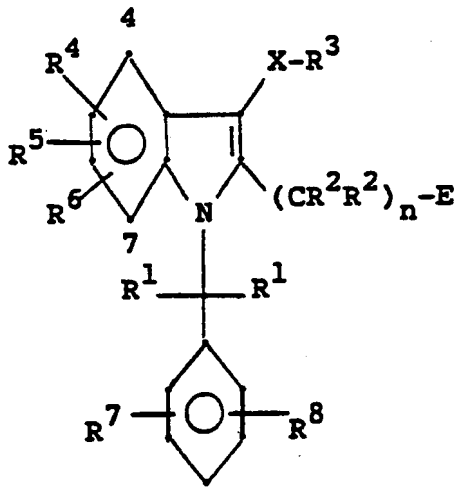
Because of their activity as leukotriene biosynthesis inhibitors, the compounds of the present invention are useful as anti-asthmatic, anti-allergic, and anti-inflammatory agents and are useful in treating allergic rhinitis and chronic bronchitis and for amelioration of skin diseases like psoriasis and atopic eczema. These compounds are also useful to inhibit the pathologic actions of leukotrienes on the cardiovascular and vascular systems for example, actions such as result in angina or endotoxin shock. The compounds of the present invention are useful in the treatment of inflammatory and allergic diseases of the eye, including allergic conjunctivitis. The compounds are also useful as cytoprotective agents and for the treatment of migraine headache.

Thus, the compounds of the present invention may also be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; inflammatory bowel disease; ethanol-induced hemorrhagic erosions; hepatic ischemic; noxious agent induced damage or necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatoxic agents such as CCl_4 and D-galactosamine; ischemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma-or stress-induced cell damage; and glycerol-induced renal failure.

The compounds of this invention are inhibitors of the biosynthesis of 5-lipoxygenase metabolites of arachidonic acid, such as 5-HPETE, 5-HETE and the leukotrienes. Leukotrienes B_4, C_4, D_4 and E_4 are known to contribute to various disease conditions such as asthma, psoriasis, pain, ulcers and systemic anaphylaxis. Thus inhibition of the synthesis of such compounds will alleviate these and other leukotriene-related disease states.

DETAILED DESCRIPTION

The compounds of this invention are best realized by Formula I:



I

wherein:

R^1 is H or loweralkyl;

R^2 is H or loweralkyl, or two R^2's may be joined to form a ring of 3-6 atoms;

R^3 is alkyl, C_2-C_6 alkenyl, substituted or unsubstituted phenyl, -$(CH_2)_m$-Het, or M-substituted alkyl;

R^4, R^5 and R^6 is each independently H, loweralkyl, C_2-C_6 alkenyl, or -$(CR^2R^2)_p$M;

R^7 and R^8 are independently H, C_1-C_3 alkyl, halogen, OH, CN, CF_3, C_1-C_3 alkoxy, C_1-C_3 alkylthio, CO_2H, C_1-C_3 alkoxycarbonyl, C_1-C_3 alkylcarbonyl, or azide;

R^9 is CF_3, loweralkyl, substituted or unsubstituted benzyl, or substituted or unsubstituted phenyl;

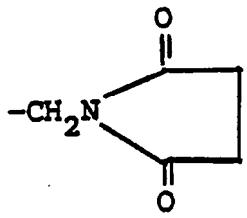
R^{10} is H, loweralkyl, unsubstituted phenyl, unsubstituted benzyl, or two R^{10}'s attached to a nitrogen may form a ring of 5 to 7 members;

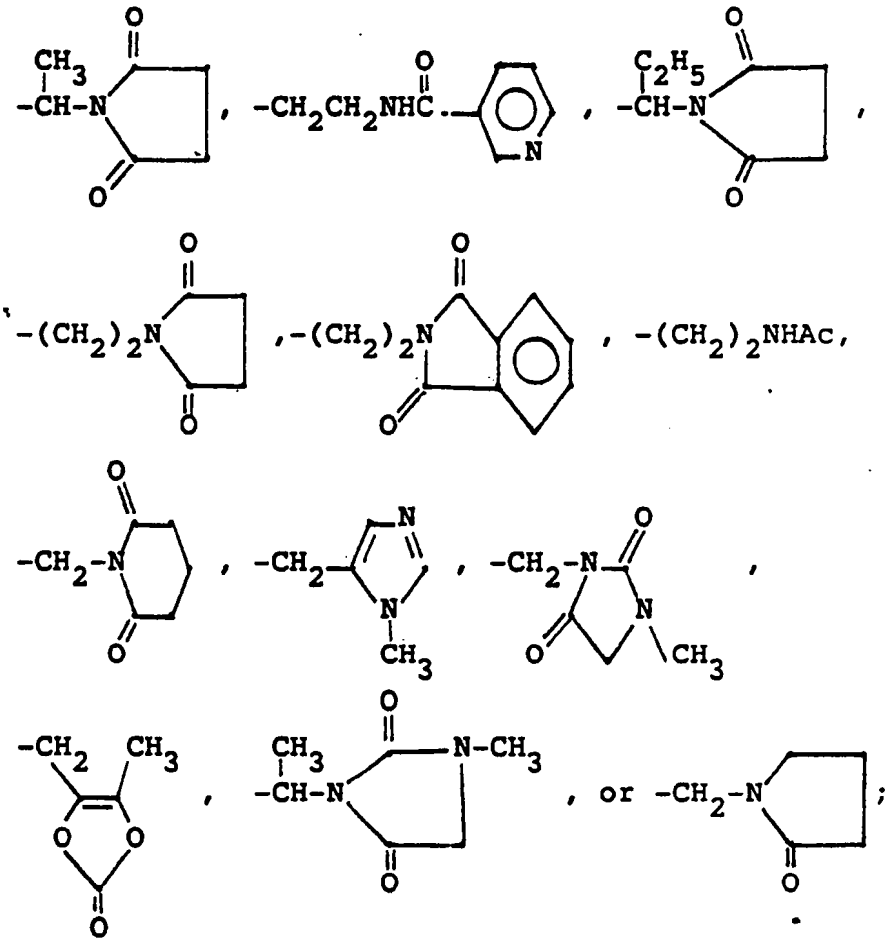
R^{11} is H or -$(CH_2)_qR^9$;

R^{12} is loweralkyl, substituted or unsubstituted benzyl, or substituted or unsubstituted phenyl;

R^{13} is H, loweralkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl;

R^{14} is -$CH_2CH_2N(R^{10})_2$, $CH_2CH(OH)CH_2OH$, -$CH_2O_2CC(CH_3)_3$, -$CH(CH_3)O_2CC(CH_3)_3$,





E is CH_2OH, CO_2R^{13}, CO_2R^{14}, tetrazol-5-yl, CHO, $C(O)NR^2R^2$, $C(O)NHS(O)_2R^9$, or $C(O)N(OR^2)R^2$;
M is a) OR^{10};
b) halogen;
c) CF_3;
d) SR^9;
e) substituted or unsubstituted phenyl;
f) $COOR^{10}$;
g) $\overset{O}{\overset{\|}{C}}-R^{11}$;
h) tetrazole;
i) $-NH-\overset{O}{\overset{\|}{C}}-R^{11}$;
j) $-NR^{10}R^{10}$;
k) $-NHSO_2R^9$;
l) $-\overset{O}{\overset{\|}{C}}-CH_2OH$;
m) $-S(O)R^9$;
n) $-CONR^{10}R^{10}$;
o) $-S(O)_2NR^{10}R^{10}$;
p) $-S(O)_2R^9$;
q) NO_2;
r) $O-\overset{O}{\overset{\|}{C}}-R^{11}$;
s) $O-\overset{O}{\overset{\|}{C}}-NR^{13}R^{10}$;

t) O-$\overset{O}{\overset{\|}{C}}$-OR'²;
u) CN;
v) N_3; or
w) H;

X is O, S, S(O), or $S(O)_2$;
m is 0-2;
n is 0-5;
p is 0-3; and
q is 0-4;

and the pharmaceutically acceptable salts thereof.

Alkyl and alkenyl are intended to include linear, branched, cyclic, and linear cyclic (e.g., alkylcycloalkyl) structures.

As used herein, the term "alkyl" includes "loweralkyl" and extends to cover carbon fragments having up to 20 carbon atoms. Examples of alkyl groups include octyl, nonyl, norbornyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, eicosyl, 3-7-ethyl-2,2-methyl-4-propylnonyl, cyclododecyl, adamantyl and the like.

As used herein, the term "loweralkyl" includes those alkyl groups of from 1 to 7 carbon atoms. Examples of loweralkyl fragments include methyl, ethyl, propyl, isopropyl, butyl, sec-and tert-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

Alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl and the like.

As used herein, the term "alkoxy" includes those alkoxy groups of from 1 to 7 carbon atoms of either a straight, branched, or cyclic configuration. Examples of alkoxy fragments include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, pentyloxy, cycloheptyloxy, and the like.

Substituted phenyl and substituted benzyl include 1 or 2 substituents on the benzene ring selected from C_1-C_3 alkyl, halogen, CN, CF_3, C_1-C_3 alkoxy, C_1-C_3 alkylthio, CO_2H, C_1-C_3 alkoxycarbonyl, C_1-C_3 alkylcarbonyl and azide.

By "Het" is meant 2-, 3-, or 4-pyridyl; tetrazolyl; 2-or 3-thienyl; 2-, 4-, or 5-thiazolyl; 2-, 4-, or 5-thiazolinyl; 1-, 2-, 4-, or 5-imidazolyl; 3-[1,2,5]-thiadiazolyl; benzothiazol-2-yl; or 2-, 3-, or 4-quinolinyl, each optionally substituted with 1 or 2 substituents selected from C_1-C_3 alkyl, halogen, CN, CF_3, C_1-C_3 alkoxy, C_1-C_3 alkylthio, CO_2H, C_1-C_3 alkoxycarbonyl, C_1-C_3 alkylcarbonyl and azide.

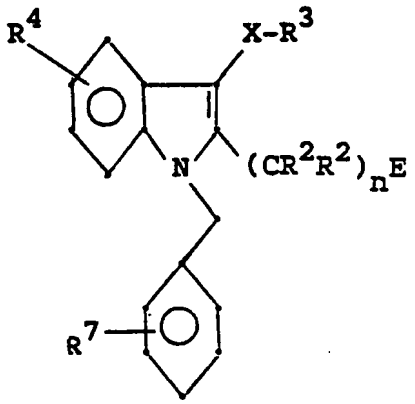
By "halogen" is meant F, Cl, Br, and I.

It is intended that the definitions of any substituent (e.g., R^2, R^4, R^5, etc.) in a particular molecule be independent of its definitions elsewhere in the molecule. Thus, $-NR^2R^2$ represents -NHH, $-NHCH_3$, $-NCH_3CH_3$, etc.

Some of the compounds described herein contain one or more centers of asymmetry and may thus give rise to diastereoisomers and optical isomers. The present invention is meant to comprehend such possible diastereoisomers as well as their racemic and resolved, optically active forms. Optically active (R) and (S) isomers may be resolved using conventional techniques.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Preferred compounds of Formula I are represented by Formula Ia:

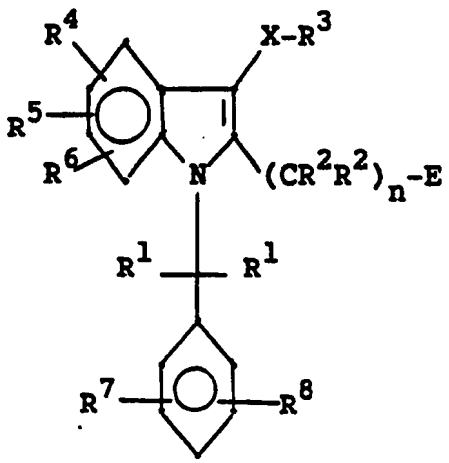


Ia

wherein:

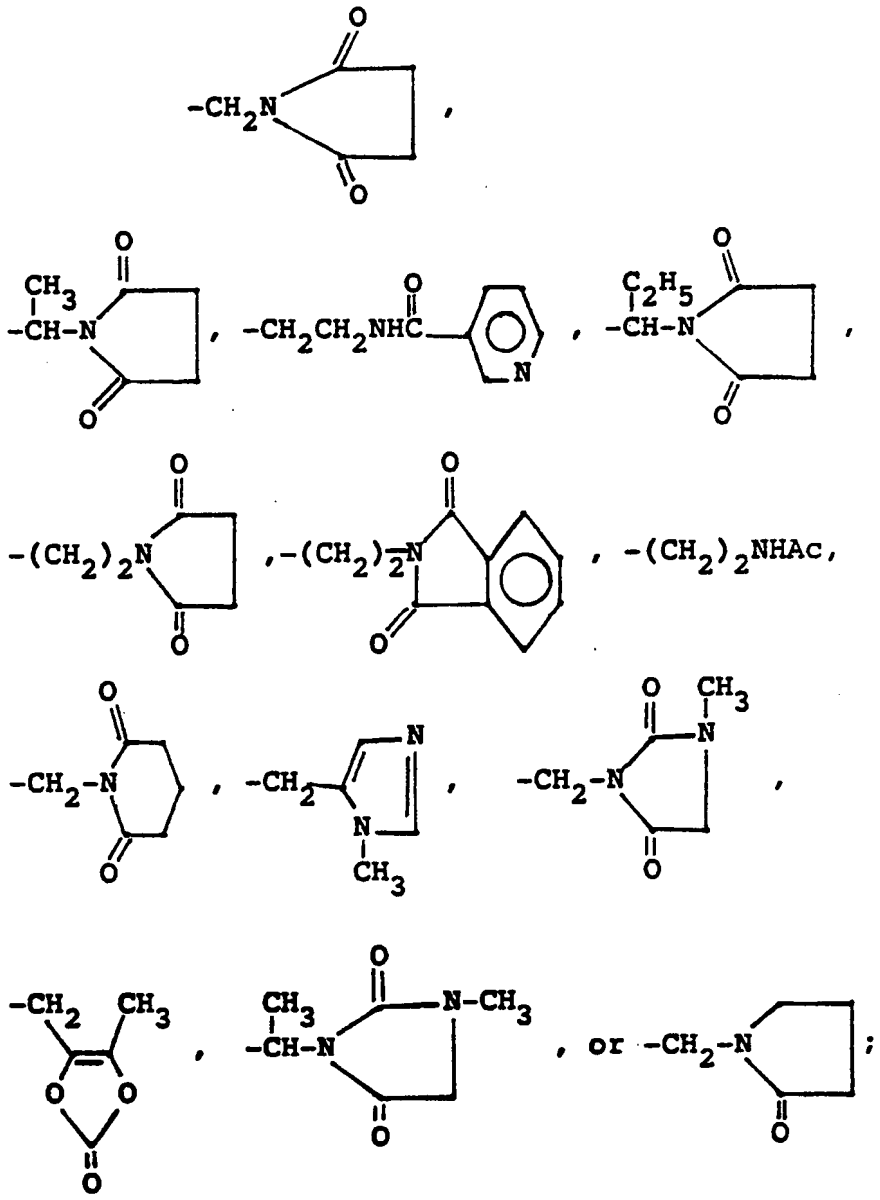
Claims

1. A compound of the formula:



I

wherein:
R^1 is H or loweralkyl;
R^2 is H or loweralkyl, or two R^2's may be joined to form a ring of 3-6 atoms;
R^3 is alkyl, C_2-C_6 alkenyl, substituted or unsubstituted phenyl, $-(CH_2)_m$-Het, or M-substituted alkyl;
R^4, R^5 and R^6 is each independently H, loweralkyl, C_2-C_6 alkenyl, or $-(CR^2R^2)_p$M;
R^7 and R^8 are independently H, C_1-C_3 alkyl, halogen, OH, CN, CF_3, C_1-C_3 alkoxy, C_1-C_3 alkylthio, CO_2H, C_1-C_3 alkoxycarbonyl, C_1-C_3 alkylcarbonyl, or azide;
R^9 is CF_3, loweralkyl, substituted or unsubstituted benzyl, or substituted or unsubstituted phenyl;
R^{10} is H, loweralkyl, unsubstituted phenyl, unsubstituted benzyl, or two R^{10}'s attached to a nitrogen may form a ring of 5 to 7 members;
R^{11} is H or $-(CH_2)_qR^9$;
R^{12} is loweralkyl, substituted or unsubstituted benzyl, or substituted or unsubstituted phenyl;
R^{13} is H, loweralkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl;
R^{14} is $-CH_2CH_2N(R^{10})_2$, $CH_2CH(OH)CH_2OH$, $-CH_2O_2CC(CH_3)_3$, $-CH(CH_3)O_2CC(CH_3)_3$,



E is CH_2OH, CO_2R^{13}, CO_2R^{14}, tetrazol-5-yl, CHO, $C(O)NR^2R^2$, $C(O)NHS(O)_2R^9$, or $C(O)N(OR^2)R^2$;

M is a) OR^{10};

b) halogen;

c) CF_3;

d) SR^9;

e) substituted or unsubstituted phenyl;

f) $COOR^{10}$;

g) $\overset{O}{\overset{\|}{C}}-R^{11}$;

h) tetrazole;

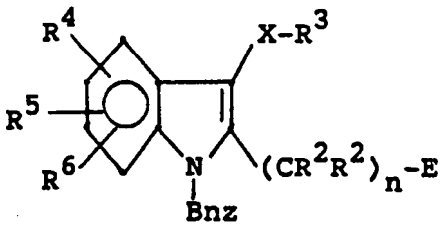
i) $-NH-\overset{O}{\overset{\|}{C}}-R^{11}$;

j) $-NR^{12}R^{10}$;

k) $-NHSO_2R^9$;

l) -C(=O)-CH_2OH;
m) -$S(O)R^9$;
n) -$CONR^{10}R^{10}$;
o) -$S(O)_2NR^{10}R^{10}$;
p) -$S(O)_2R^9$;
q) NO_2;
r) O-C(=O)-R^{11};
s) O-C(=O)-$NR^{10}R^{10}$;
t) O-C(=O)-OR^{12};
u) CN;
v) N_3; or
w) H;
X is O, S, S(O), or $S(O)_2$;
m is 0-2;
n is 0-5;
p is 0-3; and
q is 0-4;
and the pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 wherein the substituents are as follows:



Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
1.	4-Cl-Bz	Ph	5-Cl	H	H	n=0	CO_2Et	S
2.	4-Cl-Bz	Ph	5-Cl	H	H	n=0	CO_2H	S
3.	4-Cl-Bz	Me	5-F	H	H	CH_2	CO_2Et	S
4.	4-Cl-Bz	Me	5-F	H	H	CH_2	CO_2H	S
5.	4-Cl-Bz	Me	5-F	H	H	CH_2	CO_2H	SO_2
6.	4-Cl-Bz	Me	5-F	H	H	$CH(CH_3)$	CO_2H	S
7.	4-Cl-Bz	Me	5-F	H	H	$C(CH_3)_2$	CO_2H	S
8.	4-Cl-Bz	Ph	5-F	H	H	CH_2	CO_2H	S
9.	4-Cl-Bz	Ph	5-F	H	H	$CH(CH_3)$	CO_2H	S

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
10.	4-Cl-Bz	Ph	5-i-Pr	H	H	CH_2	CO_2H	S
11.	4-Cl-Bz	Ph	5-i-Pr	H	H	$CH(CH_3)$	CO_2H	S
12.	4-Cl-Bz	Ph	5-t-Bu	H	H	CH_2	CO_2H	S
13.	4-Cl-Bz	Ph	5-t-Bu	H	H	CH_2	CO_2H	SO
14.	4-Cl-Bz	Ph	5-t-Bu	H	H	CH_2	CO_2H	SO_2
15.	4-Cl-Bz	Ph	5-F	H	H	$(CH_2)_2$	CO_2H	S
16.	4-Cl-Bz	Ph	5-i-Pr	H	H	$(CH_2)_2$	CO_2H	S
17.	4-Cl-Bz	Me	5-F	H	H	$(CH_2)_2$	CO_2H	S
18.	4-Cl-Bz	Ph	5-F	H	H	$CH_2C(CH_3)_2$	CO_2H	S

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
19.	4-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
20.	4-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO
21.	4-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
22.	4-Cl-Bz	Ph	5-Ph	H	H	$CH_2C(CH_3)_2$	CO_2H	S
23.	4-Cl-Bz	Me	5-F	H	H	$CH_2C(CH_3)_2$	CO_2H	S
24.	4-Cl-Bz	Me	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
25.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
26.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO
27.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
28.	4-Cl-Bz	t-Bu	5-Ph	H	H	$CH_2C(CH_3)_2$	CO_2H	S
29.	4-Cl-Bz	Ph	5-i-Pr	H	H	$(CH_2)_2C(CH_3)_2$	CO_2H	S
30.	4-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	O
31.	4-Cl-Bz	Me	5-F	H	H	$CH_2C(CH_3)_2$	CO_2H	O
32.	4-Cl-Bz	Ph	5-i-Pr	H	H	$(CH_2)_2$	CO_2H	O
33.	4-Cl-Bz	Me	5-F	H	H	$(CH_2)_2$	CO_2H	O
34.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CH_2OH	S
35.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	$CONH_2$	S
36.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CHO	S

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
37.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CONH- $-SO_2Ph$	S
38.	4-Cl-Bz	Ph	5-i-Pr	H	H	$(CH_2)_2$	tetrazol-5-yl	S
39.	4-Cl-Bz	CH_2CH_2OH	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
40.	4-Cl-Bz	CH_2CH_2OH	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO
41.	4-Cl-Bz	CH_2CH_2OH	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
42.	4-Cl-Bz	$C(CH_3)_2CH_2CO_2H$	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
43.	4-Cl-Bz	$C(CH_3)_2CH_2CO_2Me$	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
44.	4-Cl-Bz	c-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
45.	4-Cl-Bz	c-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
46.	4-Cl-Bz	c-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
47.	4-Cl-Bz	i-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
48.	4-Cl-Bz	i-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO
49.	4-Cl-Bz	i-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
50.	4-Cl-Bz	$C(CH_3)_2CH_2OH$	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
51.	4-Cl-Bz	4-Me_2NCH_2-Ph-	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
52.	4-Cl-Bz	4-Me_2NCH_2-Ph-	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO
53.	4-Cl-Bz	4-Me_2NCH_2-Ph-	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
54.	4-Cl-Bz	t-Bu	5-c-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
55.	4-Cl-Bz	t-Bu	5-c-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO
56.	4-Cl-Bz	t-Bu	5-c-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
57.	4-Cl-Bz	2-imidazyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
58.	4-Cl-Bz	2-imidazyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO
59.	4-Cl-Bz	2-imidazyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
60.	4-Cl-Bz	4-imidazyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
61.	4-Cl-Bz	2-(1-Me-imidazyl)	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
62.	4-Cl-Bz	5-(1-Me-tetrazyl)	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
63.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2\overset{1}{C}CH_2CH_2$	CO_2H	S

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
64.	4-Cl-Bz	4-pyridyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
65.	4-Cl-Bz	2-pyridyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
66.	4-Cl-Bz	2-thiazolyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
67.	4-Cl-Bz	2-thiazolinyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
68.	4-Cl-Bz	CH_2-2-pyridyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
69.	4-Cl-Bz	CH_2-4-pyridyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
70.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	O
71.	4-Cl-Bz	t-Bu	5-Ph	H	H	$CH_2C(CH_3)_2$	CO_2H	O
72.	4-Cl-Bz	i-Pr	5-Ph	H	H	$CH_2C(CH_3)_2$	CO_2H	O

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
73.	4-Cl-Bz	i-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	O
74.	4-MeOBz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
75.	4-OHBz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
76.	3-I, 4-OHBz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
77.	3,4-di-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
78.	4-Cl-Bz	Ph	5-Et	H	7-Me	$CH_2C(CH_3)_2$	CO_2H	S
79.	4-Cl-Bz	Ph	6-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
80.	4-MeO-Bz	n-Bu	4-Me	H	6-i-Pr	$CH_2C(CH_3)_2$	CO_2H	SO_2
81.	4-Cl-Bz	t-Bu	5-OEt	H	H	$CH_2C(CH_3)_2$	CO_2H	S

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
82.	2,6-di-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
83.	4-Cl-Bz	t-Bu	5-i-Pr	H	7-Me	$CH_2C(CH_3)_2$	CO_2H	S
84.	3,5-di-Cl-Bz	Ph	5-i-Pr	H	6-Me	$CH_2C(CH_3)_2$	CO_2H	SO_2
85.	4-Cl-Bz	4-MePh	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	O
86.	4,6-di-Cl-Bz	t-Bu	5-OMe	H	4-Me	$CH_2C(CH_3)_2$	CO_2H	S
87.	4-Cl-Bz	4-NH_2-Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
88.	4-Cl-Bz	4-N_3-Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
89.	4-Cl-Bz	3-NH_2-Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
90.	4-Cl-Bz	3-NHAc-Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
91.	4-Br-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO
92.	4-Br-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
93.	4-Br-Bz	Ph	5-MeO	H	6-Me	$CH_2C(CH_3)_2$	CO_2H	SO_2
94.	4-I-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
95.	4-SMe-Bz	Ph	4-Me	5-i-Pr	7-Ac	$CH_2C(CH_3)_2$	CO_2H	S
96.	$4-S(O)_2NMe_2$	4-CN-Ph	$4-N_3$	5-OEt	7-OAc	$CH_2C(CH_3)_2$	$COCH_2OH$	S
97.	$4-S(O)_2NMe_2$	4-Tz-Ph	$4-N_3$	5-OEt	7-OAc	$CH_2C(CH_3)_2$	$COCH_2OH$	S
98.	4-Cl-Bz	Ph	$5-C(OH)(CH_3)_2$	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
99.	4-Cl-Bz	Ph	$5-CH(CH_3)CH_2OH$	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
100.	4-Cl-Bz	t-Bu	$5-C(OH)(CH_3)_2$	H	H	$CH_2C(CH_3)_2$	CO_2H	S

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
101.	4-Cl-Bz	t-Bu	5-$CH(CH_3)CH_2OH$	H	H	$CH_2C(CH_3)_2$	CO_2H	S
102.	4-Cl-Bz	n-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
103.	4-Cl-Bz	n-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
104	4-Cl-Bz	Cyclohexyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
105	4-Cl-Bz	Cyclohexyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO
106	4-Cl-Bz	Cyclohexyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
107	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	$CONHCH_2CO_2H$	S
108	4-Cl-Bz	CH_2-c-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
109	4-Cl-Bz	CH_2-c-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	$CONHCH_2CO_2H$	S
110	4-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	$CONHCH_2CO_2H$	SO_2
111	4-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	$CONHCH_2CO_2H$	S

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
112	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	$CON(Me)_2$	S
113	4-Cl-Bz	CH_2-c-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	$CONH_2$	S
114	4-OH-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
115a	4-NO_2-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2CH_3	SO_2
115b	4-NH_2-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
116	4-Cl-Bz	5-Cl-Benzo-thiazol-2-yl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
117	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH(CH_3)$	CO_2H	S
118	4-CH_3SO_2-Bz	t-Bu	5-i-Pr	7-Cl	H	$CH_2C(CH_3)_2$	CO_2H	S
119	4-Cl-Bz	CH_2-c-Pr	5-i-Pr	4-CF_3	7-Br	$CH_2C(CH_3)_2$	CO_2H	O
120	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	O

Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2R^2)_n-$	E	X
121	4-Cl-Bz	2-Quinolinyl	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
122	4-Cl-Bz	t-Bu	5-i-Pr	4-SEt	H	$CH_2C(CH_3)_2$	$CH_2OCOCH_2CO_2H$	S
123	4-Cl-Bz	t-Bu	5-i-Pr	7-COMe	H	$CH_2C(CH_3)_2$	$CH_2NHCOCH_2CO_2H$	S
124	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C-(CH_2)_3-CH_2$	CO_2H	S
125	4-MeO-Bz	4-N_3-Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
126	3-CN-Bz	t-Bu	5-i-Pr	4-$S(O)_2$-Me	H	$CH_2C(CH_3)_2$	CO_2H	S
127	4-Cl-Bz	$CH_2CH_2CH{=}CH_2$	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
128	4-Cl-Bz	Bz	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
129	4-Cl-Bz	2-(i-Pr)Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
130	4-Cl-Bz	2-(i-Pr)Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
131	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S

3. The compounds of Claim 1 which are:
ethyl 1-)p-chlorobenzyl)-5-chloro-3-thiophenylindole-2-carboxylate;
1-(p-chlorobenzyl)-5-chloro-3-thiophenylindole-2-carboxylic acid;
ethyl 1-(p-chlorobenzyl)-5-fluoro-3-methylthioindole-2-acetate;
1-(p-chlorobenzyl)-5-fluoro-3-methylthioindole-2-acetic acid;
1-(p-chlorobenzyl)-5-fluoro-3-methylsulfonylindole-2-acetic acid;
1-(p-chlorobenzyl)-5-fluro-α-methyl-3-methylthioindole-2-acetic acid;
1-(p-chlorobenzyl)-α,α-dimethyl-5-fluoro-3-methylthioindole-2-acetic acid;
1-(p-chlorobenzyl)-5-fluoro-3-phenylthioindole-2-acetic acid;
1-(p-chlorobenzyl)-5-fluoro-α-methyl-3-phenylthioindole-2-acetic acid;
1-(p-chlorobenzyl)-3-phenylthio-5-(i-propyl)-indole-2-acetic acid.
1-(p-chlorobenzyl)-α-methyl-3-phenylthio-5-(i-propyl)-indole-2-acetic acid;
1-(p-chlorobenzyl)-5-(t-butyl)-3-phenylthio-indole-2-acetic acid;
1-(p-chlorobenzyl)-5-(t-butyl)-3-phenylsulfinylindole-2-acetic acid;